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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 09/393,173 | 09/09/1999 | DAVID T. CURIEL | D6163 | 2338 |

27851 7590 08/28/2002

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| EXAMINER |
|---|
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| ART UNIT | PAPER NUMBER |
|---|---|
| 1632 | |

DATE MAILED: 08/28/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/393,173 | CURIEL ET AL. | |
| | Examiner | Art Unit | |
| | Anne M Wehbé | 1632 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *04 October 2001* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-3 and 5-10* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3 and 5-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

## DETAILED ACTION

Applicant's amendment and response received on 10/4/01 has been entered. Please note that the notice of abandonment mailed on 10/3/01 has been rescinded, and prosecution of the instant application has resumed. Claims 1-3, and 5-10 are pending in the instant application. An action on the merits follows.

Those sections of Title 35, US code, not included in this action, can be found in the previous office actions.

### *Claim Rejections - 35 USC § 112*

Claims 2-3 and 5-10 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making an inducible adenoviral vector encoding the bax gene and using said vector to express bax in tumor cells *in vitro*, does not reasonably provide enablement for the treatment of any neoplastic disease, including ovarian cancer, by administering to a mammal by any route of administration an inducible adenoviral vector encoding bax. The specification does not enable any person skilled in the art or to which it most nearly pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these

claims. Applicant's arguments have been fully considered but have not been found persuasive in overcoming the instant grounds of rejection for reasons of record as discussed in detail below.

The applicant argues that the present invention makes no claim to gene therapy. The applicant's claims 3 and 5-10 are specifically directed to methods of treating cancer in an individual using the disclosed inducible adenoviral vector encoding a bax gene. Claim 2 recites a composition for inducing apoptosis and inhibiting cell growth. This claim reads both on the inhibition of cell growth both in vitro and in vivo. The field of gene therapy encompasses the therapeutic in vivo administration of genes in the form of DNA or RNA, and in particular in the form of a vector, for the treatment of disease. Thus, applicants claims which are directed to the in vivo delivery of an adenoviral vector encoding a putative therapeutic gene, i.e. bax, are clearly directed to gene therapy, and in particular gene therapy of cancer.

The applicant further argues that the office has not provided any scientific evidence to support the finding of non-enablement. In response, it is noted that the prior office actions, in particular, the office action mailed on 12/13/99, provided a detailed scientific analysis of the specification in regards to enablement of the claimed invention. The previous office actions analyzed the specification in direct accordance to the factors outlined in *In re Wands*, namely 1) the nature of the invention, 2) the state of the prior art, 3) the predictability of the art, 4) the amount of direction or guidance present, and 5) the presence or absence of working examples, and presented detailed scientific reasons supported by publications from the prior art (see Verma et al., Crystal et al., and Anderson et al.) for the finding of a lack of enablement for the instant

methods. In addition, case law including the Marzocchi decision sanctions both the use of sound scientific reasoning and printed publications to support a holding of non-enablement (see *In re Marzocchi* 169 USPQ 367, and *Ex parte Sudilovsky* 21 USPQ2d 1702). Further, the applicant is reminded that the unpredictability of a particular art area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See *Ex parte Singh*, 17 USPQ2d 1714 (BPAI 1991). Ultimately, case law states that ".. the disclosure of an application shall inform those skilled in the art how to use applicant's alleged discovery, not to find out how to use it for themselves." *In re Gardner* 166 USPQ 138 (CCPA) 1970. The applicant's response has not addressed the scientific issues raised in the previous office actions, such as the lack of guidance provided in the specification for the parameters affecting the in vivo delivery of therapeutic amounts of a recombinant adenoviral vector encoding bax, the lack of working examples which correlate with applicant's claimed in vivo methods of treating neoplastic disease, the art recognized underdeveloped and unpredictable state of the art of gene therapy of cancer at the time of filing, and the breadth of applicant's claims. As such, the rejection of record is maintained over claims 2-3 and 5-10.

***Claim Rejections - 35 USC § 103***

The rejection of claim 1 under 35 U.S.C. 103(a) as being unpatentable over WO 96/25507, published on 8/22/96, hereafter referred to as Seth et al. in view of Massie et al. (1998)

J. Virol., Vol. 72 (3) 2289-2296, is withdrawn in view of applicant's amendment to claim 1. However, please note that applicant's amendments have resulted in the following new grounds of rejection of the claims under 35 U.S.C. 103 presented below.

Claims 1-2 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over WO 96/25507, published on 8/22/96, hereafter referred to as Seth et al. in view of Sato et al. (Sept. 1, 1998) Mol. Cell. Neurosci., Vol. 12, 65-78 and Anton et al. (1995) J. Virol., Vol. 69, No. 8, 4600-4606.

The applicant claims an inducible recombinant adenoviral vector encoding a pro-apoptotic *bax* gene , wherein coding sequence of said *bax* gene is placed downstream of a loxP excision cassette. The applicant further claims a composition comprising said adenoviral vector, a vector encoding a protein that induces the expression of the *bax* gene encoded by the adenoviral vector, and an acceptable carrier.

Seth et al. teaches the construction of an adenoviral vector which can be modified to encode a gene useful for eradicating tumor cells via the toxic effects of the expressed gene. Seth et al. teaches that genes useful for inclusion in the adenoviral vector include BAX (Seth et al., page 21, lines 27-35).

Seth et al. does not specifically teach an inducible adenoviral vector wherein the bax gene is located downstream of a loxP site. Sato et al. supplements Seth et al. by teaching an adenoviral based Cre/loxP system to express Bcl-2 in cells. Sato et al. specifically teaches the dual infection

of cells with a first recombinant adenovirus encoding Bcl-2 downstream from an excisable spacer DNA flanked by loxP sites and a second recombinant adenovirus encoding the recombinase Cre (Sato et al., page 65, and page 67, Figure 1). Following co-infection of cells, the expressed Cre recombinase mediates the excision of the loxP flanked spacer resulting in the expression of the bcl-2 gene ( Sato et al. page 67, Figure 1, and page 71, Figure 4). Sato et al. further provides motivation for using the inducible cre/loxP system for expressing genes related to cell cycle regulation by teaching that initial attempts to generate adenovirus encoding Bcl-2 failed due to expression of the Bcl-2 gene during virus replication or virus plaque formation ( Sato et al., page 74, column 2). Anton et al. further supplements both Seth et al. and Sato et al. by teaching that the adenoviral cre/loxP system can be exploited for the regulated expression of toxic gene produces in cells or animals (Anton et al., page 4605, column 2). Thus, based on the teachings of Anton et al. And Sato et al., the skilled artisan would have been motivated to use the cre/loxP adenovirus system taught by Sato et al. to express the bax gene product in order to avoid problems with cell toxicity due to expression of the apopotosis inducing bax gene. Thus, it would have been *prima facie* obvious to the skilled artisan at the time of filing to make an adenovirus encoding bax as taught by Seth et al. using the inducible adenovirus cre/loxP system taught by Sato et al. in order to improve the production of recombinant adenovirus and to prevent bax toxicity in non-target cells, such as cells used to produce the recombinant adenovirus. Further, based on the successful use of the cre/loxP system to produce adenovirus encoding bcl-2 and to selectively express bcl-2 in target cells, the skilled artisan would have had a reasonable

expectation of success in making a recombinant inducible adenovirus encoding the bax gene downstream of loxP sites.

No claims are allowed.

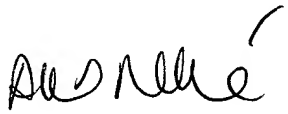
Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (703) 306-9156. The examiner can be reached Mon-Thurs and every other Friday from 9:30-7:00. If the examiner is not available, the

examiner's supervisor, Deborah Reynolds, can be reached at (703) 305-4051. General inquiries should be directed to the group receptionist whose phone number is (703) 308-0196. The technology center fax number is (703) 308-4242, the examiner's direct fax number is (703) 746-7024.

Dr. A.M.S. Wehbé



**ANNE M. WEHBE' PH.D**
**PRIMARY EXAMINER**